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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,899	03/23/2004	Steven Petrou	1386/19	2461

25297 7590 08/19/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
08/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,899	PETROU ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,21,24 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4, 21, 24, 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/25/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 2, 4, 21, 24 and 25 are pending and examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/06/2008 has been entered.

This Office Action is in reply to Applicants' correspondence of 02/06/2008.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is **NON-FINAL**.

Response to Remarks Concerning Priority

1. Applicants have traversed the Examiners finding that the effective filing date of the instant claims is 3/23/2004, the filing date of the US Application. The Examiner has set forth that the claims include the language of screening for alteration in 'a regulatory region' of the SCN1A gene, where the priority document does not support such a specific limitation. Applicants have argued that the Priority Document (i.e. Australian

application 2003901425, dated 03/27/2003) discloses methods for testing a patient for SCN1A gene mutations, where the term 'gene' is believed to encompass both regulatory and non-regulatory regions. The argument is not persuasive. While the generic term 'gene' may encompass different regions, portions, and sequence elements of the SCN1A genetic locus, the recitation of the generic term is not a basis for the specific recitation of any one particular element. There is no contemplation or specific recitation in the Priority Document to single out 'a regulatory region' for the generically taught SCN1A gene. As such the Examiner maintains that because of the recitation of the required 'a regulatory region' in the claims, the effective filing date of the claims is the filing date of the US Application, which is 03/23/2004.

With regard to the claim to priority and the recitation in the claims which require establishing whether the alteration 'would result in a major disruption to a protein', it is noted that the claims have been amended to recite 'truncating alteration' instead of 'major disruption', where the Priority Document provides a basis for truncating mutations (e.g. p.11 ln.32 of Australian application 2003901425)

Note on the Examined Limitations of Claims 4 and 21

2. A previous objection to claims 4 and 21 for the specific recitation of non-elected subject matter (i.e. claims 4 and 21 recite methods encompassing the use of SCN1A alterations as presented in Table 3, where in response to the requirement for restriction Applicant has elected for the examination of the claims in so far as they require the c251A→G nucleotide change) has been withdrawn in a previous Office Action. It is

reiterated that prior to allowance of claims, if the non-elected subject matter is not rejoined, the non-elected subject matter will be required to be deleted from the claims.

Withdrawn Claim Rejections - 35 USC § 112 2nd¶ - Indefiniteness

3. The rejection of claims 1-3, 5-17, 20, 24, and 25 under 35 USC 112 2nd ¶ as unclear over recitation of the phrase 'testing a patient sample for the existence of an alteration in the SCN1A gene', as set forth in the previous Office Action, is **WITHDRAWN** in light of the cancellation of claims and the amendments to the claims to recite 'screening a patient sample for the existence of an alteration in the SCN1A gene'. While this limitation is broad, one of skill in the art would be reasonably apprised of the metes and bounds of the claim as it requires the existence of some difference in the SCN1A gene of a patient as compared to an SCN1A gene from another source.

The rejection of claims 1-17, 20, 24, and 25 under 35 USC 112 2nd ¶ as unclear over recitation of the phrase 'known to be' in reference to whether a detected alteration is SMEI associated or non-SMEI associated, as set forth in the previous Office Action, is **WITHDRAWN** in light of the cancellation of claims and the amendments to the claims to recite an alteration 'has been previously detected in a patient clinically diagnosed with SMEI and is therefore considered SMEI associated or has been detected in a patient not diagnosed with SMEI and is therefore considered non-SMEI associated', where the skilled artisan would recognize, based on the prior art and the language to the claims, the metes and bounds of what is required for an alteration to thus be considered SMEI associated or non-SMEI associated.

The rejection of claims 2 and 25 under 35 USC 112 2nd ¶ as unclear over recitation of the phrase 'a major disruption to the protein', as set forth in the previous Office Action, is **WITHDRAWN** in light of the amendments to the claims to recite 'truncating mutation'.

The rejection of claims 1-17, 20, 21, 24, and 25 under 35 USC 112 2nd ¶ as unclear for a lacking a final process step that relates the methods steps to the purpose of the methods as recited in the preamble of the claims, as set forth in the previous Office Action, is **WITHDRAWN** in light of the amendments to the claims and the cancellation of claims.

Maintained Claim Rejections - 35 USC § 112 2nd¶ - Indefiniteness

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 4 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 21 are unclear over the recitations of the requirements 'wherein the alteration is one of the nucleotide changes identified in Table 3' (as recited in claim 4), and 'alteration as laid out in column 3 of Table 3' (as recited in claim 21), where, consonant with the election, Applicant has elected the missense mutation corresponding to the c251A→G nucleotide change. However, the phrases as written in the claims are unclear, because, when incorporating the Election of the missense

mutation corresponding to the c251A→G nucleotide change it is unclear what particular elements are required to detect the c251A→G alteration. The recitation of 'c251A→G', as recited in Table 3, Elected by Applicants, and required by the claims, does not provide where the particular required alteration occurs in any sequence (a particular transcript, gene sequence, or genetic locus with any specific number scheme). As such the skilled artisan would not recognize the metes and bounds of the limitation as required by the claim. The claim may be made more clear if amended to recite particular sequence elements associated with the elected alteration in Table 3, for example 'wherein the alteration is the presence of a G nucleotide in the SCN1A gene at a position corresponding to position 517 of SEQ ID NO: 1'.

Response to Remarks

Applicants have traversed the rejections of claim 4 and 21 under 35 USC 112 2nd ¶ as indefinite. Applicants argue (p.14-15 of Remarks) that claim 4 is limited to a nucleotide change, and that claim 21 has been amended to require 'column 3' of Table 3, where applicants argue that column 3 of Table 3 presents nucleotide changes. The arguments are not found to be persuasive. The Examiner maintains that the recitation in Table 3 as consonant with the Election does not provide any limiting definition for what sequence elements are required for the SCN1A gene or alterations thereof. As such, the recitation of c251A→G (as recited in Table 3 and consonant with the Election) is indefinite. Further it is noted that, with regard to the requirements of 35 USC 112 2nd ¶, MPEP 2173.05(s) provides:

> Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate

> by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted)

The rejection as set forth is **MAINTAINED.**

Claim Rejections - 35 USC § 112 1st¶ - Written Description Withdrawn in part, Maintained in Part

6. The rejection of claims 1-17, 20, 21,24, and 25 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, as set forth in the previous Office Action, is **WITHDRAWN IN PART** as it was applied to claims 1-3, 5-17, 20, 24, and 25 in light of the cancellation of claims and the amendments to the claims to require, for example, that an 'alteration, when one is detected, has previously been detected in a patient clinically diagnosed with SMEI and is therefore considered SMEI associated'. The skilled artisan, when detecting an alteration in the SCN1A gene, as generically required by the claims, would be able to ascertain if the alteration was previously detected in a patient clinically diagnosed with SMEI or not diagnosed with SMEI. The rejection is **MAINTANED IN PART**, as set forth below, as it was previously applied to claims 4 and 21, which require the particular alteration c251A→G as recited in TAble 3 and consonant with Applicants election of 09/28/2008.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 4 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is noted that this rejection of method claims is made over the lack of an adequate written description of the specifically required 'c251A→G' alteration required by the claims and recited in Table 3 as consonant with Applicants' Election. In the case of claims 4 and 21, the specific required alteration 'c251A→G' is a critical element of the claimed method and therefore must be adequately described.

Applicant is referred to the Written Description Training Materials revised as of March 25, 2008, available online from www.uspto.gov/web/menu/written.pdf

With specific regard to the limitations of claims 4 and 21, which, consonant with Applicants' Election, require the detection of an alteration that is described in Table 3 as a c251A→G nucleotide change, the art with regard to the numbering of nucleotides in the SCN1A gene indicate that there are different numbering systems applicable to the SCN1A gene. First, it is noted that while column 3 of Table 3 indicates a nucleotide change at position 251 in which a G is substituted for an A and further specifies that this mutation is shown in SEQ ID NO: 1, the altered position with the G content in SEQ ID NO: 1 is at position 517 of SEQ ID NO: 1. Furthermore, within the art of the SCN1A gene sequence, the altered position is at a position corresponding to position 269 in GenBank Locus AF2258985 and GenBank Locus NM_006920 (see provided sequences). Thus an adequately specific written description is not provided for a

method encompassing the identification of a 'c251A→G' alteration. The requirement for a clear written description of the required specific alteration is critical in light of the disclosure indicating that the 'c251A→G' alteration is found in a patient diagnosed with SMEI, and thus is an SMEI associated alteration, as required by the claims

Relevant to the written description requirement of 35 USC 112 1st ¶ and requirement for a particular SCN1A alteration recited as 'c251A→G', MPEP 2163 states:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art.

In the case of the instant claims, the ability to identify the required alteration from Table 3 that is 'c251A→G' and asserted in the specification to be identified in a patient diagnosed with SMEI is critical to the claimed invention. However, as detailed above, the particular nature of an alteration that is recited as 'c251A→G' is not conventional in the art, and thus the association of the mutation with SMEI is not known to the artisan of ordinary skill.

Having considered the requirement of the rejected claims, the guidance provided by the specification, and the teachings of the prior art, it is the conclusion that while the specification provides a written description of a specific alteration that is identified by the presence of a G at position 517 of SEQ ID NO: 1, there is not an adequate written description of an SMEI associated alteration that is 'c251A→G'.

Response to Remarks

Applicants have traversed the rejection of claims for lack of adequate written description. It is noted that based on the amendments to the claims, the rejection has been withdrawn from pending claims 1, 2, 24 and 25, where the skilled artisan would be able to determine if a detected alteration has been previously identified in a patient diagnosed or not diagnosed with SMEI. As the rejection has been withdrawn from these claims, Applicants arguments regarding this portion of the rejection as previously set forth are moot. Applicants' remarks (p.16-19 of Remarks) offer no traversal of the rejection at is specifically applies to the requirement of a 'c251A→G' alteration, where the Examiner has set forth that the claims require a specific alteration for the practice of the claimed methods and the specification in view of the prior art does not provide an adequate description of the required alteration (as recited Table 3 and Elected by Applicants) for the skilled artisan to practice the claimed invention.

The rejection as set forth is MAINTAINED.

Withdrawn Claim Rejections - 35 USC § 112 1st¶ - Enablement

9. The rejection of claims 1-17, 20, 21, 24 and 25 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, as set forth in the previous Office Action, is **WITHDRAWN** in light of the cancellation of claims and the amendments to the claims. It is noted that portions of the rejection as previously set forth are incorporated into the scope of enablement rejection as set forth below.

New Claim Rejection - 35 USC § 112 1st¶ - Scope of Enablement

10. Claims 1, 2, 4, 21, 24, and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A method for determining the likelihood that a human patient suspected of SMEI does or does not have SMEI comprising:
> (1) detecting the presence of an alteration in the SCN1A gene of the patient by sequencing the SCN1A gene in a patient sample;
> (2) ascertaining whether the alteration: (i) has previously been detected in a patient clinically diagnosed with SMEI and is therefore considered SMEI associated; or (ii) has previously been detected in a patient diagnosed as not having SMEI and is therefore considered non-SMEI associated; or (iii) is not known to have been either previously detected in a patient clinically diagnosed with SMEI or in a patient diagnosed as not having SMEI and is therefore not considered to be either SMEI associated or non-SMEI associated; wherein:
> (a) the patient is categorized as having a high probability of having SMEI is when the alteration is SMEI associated;
> (b) a the patient is categorized as having a low probability of having SMEI when the alteration is non-SMEI associated; or
> (c) further analysis is undertaken to establish the likelihood the patient suspected of SMEI does or does not have SMEI when the detected alteration is not considered to be either SMEI associated or non-SMEI associated, thereby establishing the likelihood that a patient suspected of SMEI does or does not have SMEI.

And (relevant to the limitations of claims 4 and 21) methods:

> Wherein the detected alteration in the SCN1A gene is an SMEI associated alteration corresponding to the presence of a G at position 517 of SEQ ID NO: 1.

The specification does not reasonably provide enablement for methods requiring establishing that a patient likely does not have SMEI when no alteration in the SCN1A gene is found (relevant to step (2)(a) in claims 1 and 21), or methods requiring determining that an alteration is non-SMEI associated if it has been previously detected in a patient not diagnosed with SMEI, or methods requiring an alteration recited as c251A→G as indicated in Table 3 and required by claims 4 and 21. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims of the instant application are drawn to methods for determining the likelihood that a patient suspected of having of SMEI does or does not have SMEI.

The claims encompass determining that a patient likely does not have SMEI if no alteration in the SCNA1 gene is found.

The claims encompass determining that an alteration is non-SMEI associated, and thus indicative of a low probability of SMEI, if the alteration has previously been detected in a patient not diagnosed with SMEI.

Claims 4 and 21, consonant with the Election, are drawn to the detection of the nucleotide change 'c251A→G'.

The claims thus require basing a determination of the likelihood that a patient has SMEI on the detection of various alterations in the SCN1A gene or a lack of a detected alteration in the SCN1A gene.

Direction provided by the specification and working example

The instant specification teaches the sequence analysis of the SCN1A gene in a study population of individuals that had been diagnosed with SMEI from a clinical analysis or had severe encephalopathies occurring during the first 12 months of life (Example 1, p.38 lns.1-5). The specification teaches the results of analysis of the 26 exons of the SCN1A gene in a total of 96 patients with the clinical epilepsy phenotype of the patients being hidden during the analysis. The

specification further teaches that of the 96 patient samples analyzed, 34 samples were shown to have an alteration in the SCN1A gene, and of those 34 samples, 28 samples were from patients with a clear SMEI phenotype based on a clinical analysis (p.41 lns.24-36). One particular alteration found in a patient diagnosed with SMEI is characterized by the presence of a G at position 517 of SEQ ID NO: 1 (i.e. the first alteration listed in Table 3). The specification further teaches the identification of 4 SCN1A alterations in patients with a non-SMEI diagnosis.

The specification uses the data from the example to draw the conclusion that 'if an SCN1A alteration is found in a patient, then the patient has an 82% chance (28/34) of having SMEI'. However, this conclusion does not consider any previous analyses of the prior art where patients diagnosed with SMEI are not found to have SCN1A alterations. Additionally, the specification does not teach whether or not any patients that were screened who were diagnoses with SMEI were found to have no SCN1A alterations.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the detection of an alteration in any particular known gene sequence is high, and the prior art teaches several examples of SCN1A gene alterations identified in patients with SMEI, there is unpredictability in drawing an association between a finding of no alterations in a patient's SCN1A gene and a diagnosis that the patients likely does not have SMEI, basing a diagnosis on an alteration that was previously found in a patient 'not diagnosed

with SMEI', or the specific identification of any particular alteration. The unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

Because the claims encompass basing a determination that a patient likely does not have SMEI on a lack of finding an alteration, it is relevant to point out the genetic heterogeneity of SMEI and the fact that patients with SMEI are often found to have no SCNA1 alterations as compared to a wild-type SCN1A gene sequence. Such findings are exemplified by Nabbout et al (2003) (Item 11 on page 2 of the IDS of 04/26/2004), which teaches that in an analysis of 93 patients with SMEI, only 33 patients (35%) had alterations on the SCN1A gene (p.1961 - Abstract; p.1965 - Table 2). As such it is highly unpredictable as to whether or not one would be able to reliable deduce that a patient likely does not have SMEI merely by finding a lack of SCN1A alterations in the SCN1A gene of the patient.

Because the claims encompass basing a determination that a patient has a low probability of having SMEI on the identification in a patient of an alteration previously detected in a patient broadly required to be 'not diagnosed with SMEI' it is relevant to point out the distinction between 'a patient diagnosed as not having SMEI' (as recited in the indicated enabled subject matter) and 'a patient not diagnosed with SMEI' (as recited in the instant claims). The instant claims encompass, for example, basing a conclusion on an alteration that was identified in another individual where no diagnosis was rendered with the other individual (e.g. in a screen for polymorphisms, but wuth no diagnostic component). The recitation in the claim encompasses a mere lack of any diagnosis, where given the teaching of the prior art that many mutations in SCN1A are

associated with SMEI, the lack of a diagnosis if considerably different than a positive diagnosis of non-SMEI.

Because the claims encompass the specific detection in a patient of an alteration from Table 3 that is identified in Table 3 as being found in a patient diagnosed with SMEI, thus indicating a high probability of SMEI, it is relevant to point out the unpredictability in associating any particular different alteration in SCN1A with the likelihood of SMEI. Such unpredictability is taught by Wallace (2005), which indicates that different SCN1A alterations may associated with different clinical phenotypes (p.19 Table 1), including non -SMEI phenotypes. It is thus unpredictable as to how any possible mutations identified as 'c251A→G' (where the recitation does not specify particular nucleotide content in a specific nucleotide context) would reliably be used in a method for determining the likelihood that a human patient suspected of SMEI does or does not have SMEI.

Quantity of experimentation required

A large amount of experimentation would be required to make and use the claimed invention in the full scope of the claims. In order to use the claimed method one would have to determine that a lack of any SCN1A alteration reliably indicates that a patient likely does not have SMEI. Given the teachings of the prior art that many SMEI patients in fact do not possess SCN1A alterations, such a determination would require identification and further analysis of other genes and genomic loci involved in the development of SMEI when no SCN1A alterations are present. Such a determination would require large genomic analyses of case:control populations and

familial pedigrees. Further, given the breadth of the required 'c251A→G' alteration that is identified in the specification as SEMI-associated and thus indicative of a high probability of SMEI, one would have to establish that any alteration that can be considered 'c251A→G' (e.g. in any transcript or genomic numbering scheme) is in fact associated with SMEI.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance of the specification and the specific working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope as claimed.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement (Remarks p.19-23). Initially it is noted that the rejection as set forth in the previous Office Action has been modified as presented in the instant Office Action in light of the cancellation of Claims and the amendments to the claims.

Applicants' traversal (pages 20-23 of Remarks) largely details the various steps of the claimed methods and how applicant proposes to use the claimed methods, but the traversal does not address the issues of enablement as detailed in the rejection.

Applicants' arguments support the rejection as set forth in the rejection. For example, Applicants point out that SMEI does not have a single cause, and that mutations in SCN1A can be linked with other diseases and not causative of SMEI. These points are particularly relevant to the breadth of the claims and the rejection as set forth. As Applicants' point out that SMEI does not have a single cause, it is unpredictable as to how one would reliably determine that a patient likely does not have SMEI merely when no alteration in SCN1A is found. Similarly, as detailed in the rejection, that an alteration in a patient is also found in a subject 'not diagnosed with SMEI' is not evidence that the detected mutation would be indicative of a low probability of SMEI, because 'not diagnosed with SMEI' doesn't provide for a positive 'non-SMEI' association.

The rejection as set forth is **MAINTAINED**.

Maintained Claim Rejections - 35 USC § 103 - Obviousness

The Examiner has rejected the claims of the instant application for a lack of enablement under 35 USC 112 1st¶. The claims are also rejected under 35 USC 103 as obvious in view of the cited prior art. In the analysis of the claimed methods it is noted that methods have multiple steps which are conditional upon the results of previous steps of the claimed methods, as such these conditional steps are in fact optional given the specific results of performing the claimed method. For example, the limitations of the method as claimed in claim 1 a met by a method comprising screening for an alteration in SCN1A, and establishing that the patient has a high probability of having SMEI when an alteration is found that has previously been detected in a patient clinically diagnosed with SMEI. In fact it is this portion of the independent claim that is rendered obvious by the prior art, where the prior art is replete with references that

provide the same analysis of SCN1A and SMEI patients as performed in the instant specification, and the same prior art reaches the same conclusions as set forth in the specification, namely that certain de novo mutations in the SCN1A gene are identified in patients with SMEI and are associated with SMEI.

For example, in view of the teachings of Claes et al (as cited in the following rejection) it would be obvious for the skilled artisan to perform a method in which the SCN1A gene of a patient suspected of having SMEI is screened for an alteration by sequencing the gene (relevant to step 1 of claim 1) and identification of the c.664C→T mutation (as disclosed in Table 2 of Claes et al as being a mutation in an SMEI patient) as an alteration that 'has previously been detected in a patient clinically diagnosed with SMEI and is therefore considered SMEI associated' results in a diagnosis of a high probability of SMEI (relevant to step 3 and part a of step 3of claim 1). Such a method, as rendered obvious by the teachings of Claes et al satisfies the limitations of claim 1.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1, 2, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Claes et al (2001).

Claes et al teaches the analysis of mutations in the SCN1A gene and the relation of the mutations to SMEI.

Regarding claim 1, Claes et al teaches testing a patient sample for the existence of an alteration in the SCN1A gene (p.1329 – SCN1A mutation analysis), as required by step (1), and identifying the nature of the mutation as required by step (2) part (b) (p.

1329 - Table 2). Relevant to step (3) and step (3)(a), the reference establishes that the particular mutations of Table 2 of the reference are detected in patients clinically diagnosed with SMEI, and thus are considered SMEI associated. Regarding the limitation of step (1) of claim 1 that the screening for the existence of an alteration is 'by sequencing the SCN1A gene', Claes et al teaches (p.1328 – Mutation detection and molecular–genetic analysis) that exon of the SCN1A gene were sequenced. Consistent with the broadest reasonable interpretation of the requirement of 'sequencing the SCN1A gene', the sequence analysis of Claes et al is 'sequencing the SCN1A gene'.

Regarding claims 2, Claes et al teaches the identification of frameshift mutations that create premature stop codons (Table 2), which is establishing that the detected alteration is a truncation mutation that would result in a major disruption to the protein.

Regarding claims 24 and 25, the reference teaches determining whether mutations were present in either of the unaffected parents (thus considering genetic data for parents, relevant to step (a) of claim 24), and determining that a mutation was absent from the parents (thus establishing that the mutation has arisen de novo) (p.1329, right col., last ¶). Relevant to claim 25, the reference teaches that *de novo* mutations are probably a major cause of SMEI.

While Claes et al teaches the analysis of the SCN1A gene in patients, Claes et al does not *per se* perform a method of determining the likelihood that a patient suspected of having SMEI does have SMEI. However, it would be obvious to incorporate the teachings and conclusions of Claes et al to create the likelihood determination methods of the instant claims.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the explicit teachings of Claes et al to perform an analysis of a patient suspected of SMEI that meets the required limitations of the rejected claims. Given the teachings of Claes et al it would be obvious to screen for an alteration in the SCN1A gene of a patient where upon the identification of any of the mutations of Table 2 of Claes et al, the skilled artisan would recognize such a mutation as an alteration that has been previously detected in a patient clinically diagnosed with SMEI and provide a determination that there is a high probability that such a patient has SMEI. One would be motivated to perform a method of determining the likelihood that patient suspected of having SMEI does or does not have SMEI using the techniques and teachings of Claes et al based on the teaching of Claes et al that particular mutations in the SCN1A gene are indicative of SMEI (p.1330 –Discussion) where the skilled artisan would recognize the diagnostic properties of identifying such a mutation in a patient.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 103 as obvious in view of the teachings of Cleas et al. Applicants arguments (p.23-26 of Remarks) have been fully and carefully considered but are not found to be persuasive.

Applicants initially argue that (p.24-25 of Remarks) Claes et al does not teach or suggest the methodology of the present claims. Applicants argue that the teachings of Claes et al, with hindsight, start to lead to the realization that a conventional test was not possible, and that it would be counterintuitive to screen the whole gene for

mutations and categorize them as set forth in the claims. The argument is not persuasive. Initially it is noted that the claims do not in fact require any step to 'screen the whole gene'. The examiner maintains that given the teachings of Claes et al (p.1330 - Discussion) that SMEI has a genetic etiology and de novo mutation are probably a major cause of SMEI, the skilled artisan would be motivated to analyze the SCN1A gene for alterations in a method of analyzing the likelihood that a patient suspected of having SMEI does or does not have SMEI. The skilled artisan would recognize that the teachings of Claes et al are not a teaching that only the specific mutations disclosed in Claes et al are associated with SMEI, but in general de novo mutations are associated with SMEI, where the teachings of Claes et al would render obvious to the skilled artisan an analysis of the whole SCN1A gene for de novo alterations in any patient suspected of having SMEI (relevant to Applicants arguments of page 25 of Remarks). However it is maintained that even the specific teachings of Claes et al with regard to particular mutations render obvious the methods of the instant claims, where the skilled artisan would recognize, based on the particular mutations taught by Claes et al, the identification in a patient suspected of having SMEI of any of the particular mutations taught by Claes et al would lead to the conclusion that the patient suspected of having SMEI has a high probability of having SMEI.

And while Applicants argue that the claimed methods are a 'gene up' approach that is somehow distinct from the teachings of the prior art (p.25) it is noted that in fact the same methodologies are disclosed in the instant specification as taught in the prior art. Both Claes et al and the instant specification: (i) create amplicons of all the exons

of the SCN1A gene from patient genomic DNA; (ii) compare the patient exons to wild-type exons using DHPLC; and (iii) perform sequence analysis on any exons considered to contain alterations, as based on the DHPLC analysis, to determine the nature of the sequence alteration in the exon.

The rejection as set forth is **MAINTAINED.**

Withdrawn Claim Rejections - 35 USC § 103

12. The rejection of claims 11, 13-15, and 17 under 35 U.S.C. 103(a) as being unpatentable over Claes et al in view of Wong et al, as set forth in the previous Office Action, is **WITHDRAWN** in light of the cancellation claims 11, 13-15, and 17.

Conclusion

13. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Stephen Kapushoc/
Art Unit 1634